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L10: Entry 4 of 5 File: USPT Sep 24, 1996

DOCUMENT-IDENTIFIER: US 5558863 A
TITLE: Method for treatment of herpes virus infections

Brief Summary Text (16):
Nasopharyngeal carcinoma has been associated with Epstein-Barr viral antigens. Patients with nasopharyngeal carcinoma have been shown to exhibit antibodies to soluble Epstein-Barr virus antigens. In addition, antibody titers in patients suffering from nasopharyngeal carcinoma appear when tumor growth is progressive and the same antibodies are frequently not detectable when tumors are regressing (see Piessens, W. F., Cancer, (Phila) 26, p. 1214 (1970)).

Brief Summary Text (24):
In practice, the present invention comprises the partitional administration of an amount not to exceed approximately 10.sup.-2 mg, although, in certain cases, the total amount of neuraminidase administered in any one day may exceed the preferred limit. The neuraminidase can be administered as a liquid or it can be administered as a solid wherein the neuraminidase is embedded or admixed in a biodegradable or bioerodable matrix. The matrix can be a time release matrix. These matrices are well known to those of ordinary skill in the art and are not critical to the present invention. The neuraminidase can be administered by injection or by sublingual route. In one embodiment, the vehicle is an aqueous solution that is contained within an inert container. In another variation, the composition is in the form of a suppository. The liquid form of the composition can be injected subcutaneously, intramuscularly or intravenously. In addition, the composition can be administered through the muscosal membranes such as nasal membranes.

Brief Summary Text (40):
Transport of many viruses and bacteria through cell mucin on the cell surface into the cell appears to be facilitated by the reaction of neuraminidase on its cell surface. The reaction by neuraminidase on the cell surface cleaves the sialic acid component, which also destroys a hemagglutinin receptor site on the host cell (see J. N. Varghese, W. G. Laver, and P. M. Colman, Nature (London) 303, pp. 35-40 (1983)). When the sialic acid component is present on the cell surface, it can stabilize certain cells through an increase in cellular adhesiveness (see L. Berwick and D. R. Coman, Cancer Res. 22, pp. 982-986) or other cells through facilitation of cellular mobilization (see M. M. Yarnell and E. J. Ambrose, Eura. J. Cancer 5, pp. 265-269 (1969)).

Brief Summary Text (44):
The neuraminidase can be administered through standard methods, including intravenous, intramuscular, and subcutaneous routes. The neuraminidase can also be administered by sublingual and intranasal routes. Because the effective amount of neuraminidase in a dose is so low, the composition according to the present invention can also be administered transdermally, anally or orally. The dosage units can be either liquid or solid. Typically, the dosage unit may be administered up to a maximum of about 15 times per day.

Detailed Description Text (3):
A 40 year old female subject was treated with the therapeutic agent for oral herpes infection. The patient received a sublingual dose of 10.sup.-4 mg neuraminidase (Sigma Chemical Company, St. Louis, Mo.) in a 50 microliter dosage of 0.1% phenol in 0.9% NaCl at fifteen minute intervals for two and one half hours, by which time the

lesion pain fully disappeared. The following morning, lesion pain returned so the treatment is reinitiated. After a two hour treatment period, the lesion pain again disappeared. The herpes lesions healed within a few days and did not reoccur as frequently (monthly) as they had during the previous twenty years.

Detailed Description Text (5):
A 37 year old male subject had shingles with severe associated pain for about one month prior to initiation of treatment with the therapeutic agent. The pain subsided dramatically after twelve hourly sublingual 50 microliter dosings of 10.sup.-4 mg neuraminidase in 0.1% phenol in 0.9% NaCl. The patient was pain-free for three days following the first treatment phase. Slight pain was experienced on the fourth day at which time he started sublingual administration every fifteen minutes for two hours. After this treatment, pain subsided. He was placed on a maintenance treatment regime of one dose per day for three weeks. He has remained completely free of shingles associated symptoms during the seventeen months of follow-up observation.

Detailed Description Text (15):
Three patients, ages 45, 53 and 67, were treated for chronic fatigue syndrome, a disease associated with the Epstein-Barr virus. Neuraminidase was administered at a dose of 10.sup.-4 mg sublingually 3 times a day for 3 days. All three patients showed marked improvement with this regimen.

Detailed Description Text (17):
A patient with nasopharyngeal carcinoma which is associated with Epstein-Barr virus, underwent surgery with subsequent radiation and chemotherapy. The treatments failed to halt the spread and growth of the tumor. Administration of neuraminidase (4 doses daily) was begun followed one week later by cyclophosphamide therapy. After 3 weeks of neuraminidase treatment, there were indications that symptoms of severe peripheral neuropathy, brought about by the chemotherapy, were being reversed.

Other Reference Publication (3):
Yarnell, M. M. et al., "Studies of Tumour Invasion in Organ Culture--II. Effects of Enzyme Treatment," Europ. J. Cancer, vol. 5, pp. 265-269 (1969).

Other Reference Publication (6):
Berwick, L. et al., "Some Chemical Factors in Cellular Adhesion and Stickiness," Cancer Research, vol. 22, pp. 982-987 (Sep. 1962).

Other Reference Publication (9):
Santoli, D. et al., "Mechanisms of Activation of Human Natural Killer Cells Against Tumor and Virus-Infected Cells," Immunological Review, vol. 44, pp. 125-163.

Other Reference Publication (20):
Trinchieri, G. et al., "Anti-Viral Activity Induced by Culturing Lymphocytes with Tumor-Derived or Virus-Transformed Cells," J. Exp. Med., pp. 1299-1313.

Other Reference Publication (26):
Welsh, R. M., "Natural Cell-Medicated Immunity During Viral Infections," Natural Resistance to Tumors and Viruses, edited by O. Haller, published by Springer-Verlag, pp. 83-106.

Other Reference Publication (29):
Lung, M. L. et al., "Detection of Distinct Epstein-Barr Virus Genotypes in NPC Biopsies from Southern Chinese and Caucasians," Int. J. Cancer, vol. 52 (1), pp. 34-37 (1992) Abstract.

L10: Entry 3 of 5 File: USPT Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736133 A
TITLE: Method and composition for the treatment of a individual infected with an immunodeficiency virus

Brief Summary Text (16):
Nasopharyngeal carcinoma has been associated with Epstein-Barr viral antigens. Patients with nasopharyngeal carcinoma have been shown to exhibit antibodies to soluble Epstein-Barr virus antigens. In addition, antibody liters in patients suffering from nasopharyngeal carcinoma appear when tumor growth is progressive and the same antibodies are frequently not detectable when tumors are regressing (see Piessens, W. F., Cancer, (Phila) 26, p. 1214 (1970)).

Brief Summary Text (24):
In practice, the present invention comprises the partitional administration of an amount not to exceed approximately 10.sup.-2 mg, although, in certain cases, the total amount of neuraminidase administered in any one day may exceed the preferred limit. The neuraminidase can be administered as a liquid or it can be administered as a solid wherein the neuramindase is embedded or admixed in a biodegradable or bioerodable matrix. The matrix can be a time release matrix. These matrices are well known to those of ordinary skill in the art and are not critical to the present invention. The neuramindase can be administered by injection or by sublingual route. In one embodiment, the vehicle is an aqueous solution that is contained within an inert container. In another variation, the composition is in the form of a suppository. The liquid form of the composition can be injected subcutaneously, intramuscularly or intravenously. In addition, the composition can be administered through the muscosal membranes such as nasal membranes.

Brief Summary Text (40):
Transport of many viruses and bacteria through cell mucin on the cell surface into the cell appears to be facilitated by the reaction of neuraminidase on its cell surface. The reaction by neuraminidase on the cell surface cleaves the sialic acid component, which also destroys a hemagglutinin receptor site on the host cell (see J. N. Varghese, W. G. Laver, and P. M. Colman, Nature (London) 303, pp. 35-40 (1983)). When the sialic acid component is present on the ceil surface, it can stabilize certain cells through an increase in cellular adhesiveness (see L. Berwick and D. R. Coman, Cancer Res. 22, pp. 982-986) or other cells through facilitation of cellular mobilization (see M. M. Yarnell and E. J. Ambrose, Eura. J. Cancer 5, pp. 265-269 (1969)).

Brief Summary Text (44):
The neuraminidase can be administered through standard methods, including intravenous, intramuscular, and subcutaneous routes. The neuraminidase can also be administered by sublingual and intranasal routes. Because the effective amount of neuraminidase in a dose is so low, the composition according to the present invention can also be administered transdermally, anally or orally. The dosage units can be either liquid or solid. Typically, the dosage unit may be administered up to a maximum of about 15 times per day.

Detailed Description Text (2):
A 40 year old female subject was treated with the therapeutic agent for oral herpes infection. The patient received a sublingual dose of 10.sup.-4 mg neuraminidase (Sigma. Chemical Company, St. Louis, Mo.) in a 50 microliter dosage of 0.1% phenol

in 0.9% NaCl at fifteen minute intervals for two and one half hours, by which time the lesion pain fully disappeared. The following morning, lesion pain returned so the treatment is reinitiated. After a two hour treatment period, the lesion pain again disappeared. The herpes lesions healed within a few days and did not reoccur as frequently (monthly) as they had during the previous twenty years.

Detailed Description Text (4):
A 37 year old male subject had shingles with severe associated pain for about one month prior to initiation of treatment with the therapeutic agent. The pain subsided dramatically after twelve hourly sublingual 50 microliter dosings of 10.sup.-4 mg neuraminidase in 0.1% phenol in 0.9% NaCl. The patient was pain-free for three days following the first treatment phase. Slight pain was experienced on the fourth day at which time he started sublingual administration every fifteen minutes for two hours. After this treatment, pain subsided. He was placed on a maintenance treatment regime of one dose per day for three weeks. He has remained completely free of shingles associated symptoms during the seventeen months of follow-up observation.

Detailed Description Text (14):
Three patients, ages 45, 53 and 67, were treated for chronic fatigue syndrome, a disease associated with the Epstein-Barr virus. Neuraminidase was administered at a dose of 10.sup.-4 mg sublingually 3 times a day for 3 days. All three patients showed marked improvement with this regimen.

Detailed Description Text (16):
A patient with nasopharyngeal carcinoma which is associated with Epstein-Barr virus, underwent surgery with subsequent radiation and chemotherapy. The treatments failed to halt the spread and growth of the tumor. Administration of neuraminidase (4 doses daily) was begun followed one week later by cyclophosphamide therapy. After 3 weeks of neuraminidase treatment, there were indications that symptoms of severe peripheral neuropathy, brought about by the chemotherapy, were being reversed.

Other Reference Publication (5):
Lung et al., Int. J. Cancer 52(1): 34-37 (1992).

Other Reference Publication (9):
Yarnell, M.M. et al., "Studies of tumor Invasion in Organ Culture-II. Effects of Enzyme Treatment," Europ. J. Cancer, vol. 5, pp. 265-269 (1969).

Other Reference Publication (12):
Berwick, L., et al., "Some Chemical Factors in Cellular Adhesion and Stickness," Cancer Research, vol. 22, pp. 982-987 (Sep. 1962).

Other Reference Publication (15):
Santoli, D. et al., "Mechanism of Activation of Human Natural Killer Cells Against Tumor and Virus-Infected Cells," Immunological Review, vol. 44, pp. 125-163 (1979).

Other Reference Publication (26):
Trinchieri, G. et al., "Anti-Viral Activity Induced by Culturing Lymphocytes with Tumor-Derived or Virus-Transformed Cells," J. Exp. Med., vol. 147, pp. 1299-1313 (1978).

Other Reference Publication (34):
Lung, M.L. et al., "Detection of Distinct Epstein-Barr Virus Genotypes in NPC Biopsies from Southern Chinese and Caucasians," Int. J. Cancer, vol. 52(1), pp. 34-37 (1992) Abstract.

Other Reference Publication (36):
Welsh, R.M., "Natural Cell-Medicated Immunity During Viral Infections," Natural Resistance to Tumors and Viruses, edited by O. Haller, published by Springer-Verlag, pp. 83-106 (1981).

CLAIMS:

6. The method of claim 1, wherein neuraminidase is administered by subcutaneous, intramuscular or intravenous injection, sublingually or transdermally.

14. The composition of claim 8, wherein the neuraminidase is administered by subcutaneous, intramuscular or intravenous injection, sublingually or transdermally.

L11: Entry 17 of 20 File: USPT Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736133 A
TITLE: Method and composition for the treatment of a individual infected with an immunodeficiency virus

Brief Summary Text (16):
Nasopharyngeal carcinoma has been associated with Epstein-Barr viral antigens. Patients with nasopharyngeal carcinoma have been shown to exhibit antibodies to soluble Epstein-Barr virus antigens. In addition, antibody liters in patients suffering from nasopharyngeal carcinoma appear when tumor growth is progressive and the same antibodies are frequently not detectable when tumors are regressing (see Piessens, W. F., Cancer, (Phila) 26, p. 1214 (1970)).

Brief Summary Text (24):
In practice, the present invention comprises the partitional administration of an amount not to exceed approximately 10.sup.-2 mg, although, in certain cases, the total amount of neuraminidase administered in any one day may exceed the preferred limit. The neuraminidase can be administered as a liquid or it can be administered as a solid wherein the neuramindase is embedded or admixed in a biodegradable or bioerodable matrix. The matrix can be a time release matrix. These matrices are well known to those of ordinary skill in the art and are not critical to the present invention. The neuramindase can be administered by injection or by sublingual route. In one embodiment, the vehicle is an aqueous solution that is contained within an inert container. In another variation, the composition is in the form of a suppository. The liquid form of the composition can be injected subcutaneously, intramuscularly or intravenously. In addition, the composition can be administered through the muscosal membranes such as nasal membranes.

Brief Summary Text (40):
Transport of many viruses and bacteria through cell mucin on the cell surface into the cell appears to be facilitated by the reaction of neuraminidase on its cell surface. The reaction by neuraminidase on the cell surface cleaves the sialic acid component, which also destroys a hemagglutinin receptor site on the host cell (see J. N. Varghese, W. G. Laver, and P. M. Colman, Nature (London) 303, pp. 35-40 (1983)). When the sialic acid component is present on the ceil surface, it can stabilize certain cells through an increase in cellular adhesiveness (see L. Berwick and D. R. Coman, Cancer Res. 22, pp. 982-986) or other cells through facilitation of cellular mobilization (see M. M. Yarnell and E. J. Ambrose, Eura. J. Cancer 5, pp. 265-269 (1969)).

Detailed Description Text (16):
A patient with nasopharyngeal carcinoma which is associated with Epstein-Barr virus, underwent surgery with subsequent radiation and chemotherapy. The treatments failed to halt the spread and growth of the tumor. Administration of neuraminidase (4 doses daily) was begun followed one week later by cyclophosphamide therapy. After 3 weeks of neuraminidase treatment, there were indications that symptoms of severe peripheral neuropathy, brought about by the chemotherapy, were being reversed.

Other Reference Publication (5):
Lung et al., Int. J. Cancer 52(1): 34-37 (1992).

Other Reference Publication (9):
Yarnell, M.M. et al., "Studies of tumor Invasion in Organ Culture-II. Effects of

Enzyme Treatment," Europ. J. Cancer, vol. 5, pp. 265-269 (1969).

Other Reference Publication (12):
Berwick, L., et al., "Some Chemical Factors in Cellular Adhesion and Stickness," Cancer Research, vol. 22, pp. 982-987 (Sep. 1962).

Other Reference Publication (15):
Santoli, D. et al., "Mechanism of Activation of Human Natural Killer Cells Against Tumor and Virus-Infected Cells," Immunological Review, vol. 44, pp. 125-163 (1979).

Other Reference Publication (26):
Trinchieri, G. et al., "Anti-Viral Activity Induced by Culturing Lymphocytes with Tumor-Derived or Virus-Transformed Cells," J. Exp. Med., vol. 147, pp. 1299-1313 (1978).

Other Reference Publication (34):
Lung, M.L. et al., "Detection of Distinct Epstein-Barr Virus Genotypes in NPC Biopsies from Southern Chinese and Caucasians," Int. J. Cancer, vol. 52(1), pp. 34-37 (1992) Abstract.

Other Reference Publication (36):
Welsh, R.M., "Natural Cell-Mediated Immunity During Viral Infections," Natural Resistance to Tumors and Viruses, edited by O. Haller, published by Springer-Verlag, pp. 83-106 (1981).

L11: Entry 18 of 20 File: USPT Feb 3, 1998

DOCUMENT-IDENTIFIER: US 5714509 A
TITLE: Inhibitors of bacterial sialidase and methods of making and using the same

Brief Summary Text (5):
Sialidases (acylneuraminyl hydrolases, EC 3.2.1.18), also known as neuraminidases, are enzymes which cleave the .alpha.-ketosidic bond between a terminal sialic acid residue and an aglycon moiety. The aglycon is usually the penultimate sugar residue of a glycoconjugate or glycoprotein carbohydrate chain. The first sialidase was purified and characterized from the influenza virus and the bacteria Vibrio cholerae [Gottschalk, A. (1957). Neuraminidase: The Specific Enzyme of Influenza Virus and Vibrio cholerae. Biochim Biophys Acta., 23, pp. 645-646]. Today, sialidases specific for varying ketosidic linkages have been identified in viruses, bacteria, parasites, and mammals. They play a critical role in viral, bacterial, and protozoa biology by mediating metabolism, adherence, and infection, and are important regulators of alternate complement pathway activation, red blood call destruction, cell growth, cell adhesion, and tumor metastasis in mammalian systems.

Detailed Description Text (141):
c) Pseudomonas aeruginosa infection in cystic fibrosis (CF) [Cacalano, G., Kays, M., Saiman, L. & Prince, A. (1992). Production of the Pseudomonas aeruginosa neuraminidase is increased under hyperosmolar conditions and is regulated by genes involved in alginate expression. Journal of Clinical Investigation 89(6), 1866-74]. Modes of delivery: oral pill, intravenous solution, nasal aerosol;

L8: Entry 4 of 8 File: USPT Sep 24, 1996

DOCUMENT-IDENTIFIER: US 5558863 A
TITLE: Method for treatment of herpes virus infections

Brief Summary Text (24):
In practice, the present invention comprises the partitional administration of an amount not to exceed approximately 10.sup.-2 mg, although, in certain cases, the total amount of neuraminidase administered in any one day may exceed the preferred limit. The neuraminidase can be administered as a liquid or it can be administered as a solid wherein the neuraminidase is embedded or admixed in a biodegradable or bioerodable matrix. The matrix can be a time release matrix. These matrices are well known to those of ordinary skill in the art and are not critical to the present invention. The neuraminidase can be administered by injection or by sublingual route. In one embodiment, the vehicle is an aqueous solution that is contained within an inert container. In another variation, the composition is in the form of a suppository. The liquid form of the composition can be injected subcutaneously, intramuscularly or intravenously. In addition, the composition can be administered through the muscosal membranes such as nasal membranes.

Brief Summary Text (44):
The neuraminidase can be administered through standard methods, including intravenous, intramuscular, and subcutaneous routes. The neuraminidase can also be administered by sublingual and intranasal routes. Because the effective amount of neuraminidase in a dose is so low, the composition according to the present invention can also be administered transdermally, anally or orally. The dosage units can be either liquid or solid. Typically, the dosage unit may be administered up to a maximum of about 15 times per day.

Detailed Description Text (3):
A 40 year old female subject was treated with the therapeutic agent for oral herpes infection. The patient received a sublingual dose of 10.sup.-4 mg neuraminidase (Sigma Chemical Company, St. Louis, Mo.) in a 50 microliter dosage of 0.1% phenol in 0.9% NaCl at fifteen minute intervals for two and one half hours, by which time the lesion pain fully disappeared. The following morning, lesion pain returned so the treatment is reinitiated. After a two hour treatment period, the lesion pain again disappeared. The herpes lesions healed within a few days and did not reoccur as frequently (monthly) as they had during the previous twenty years.

Detailed Description Text (5):
A 37 year old male subject had shingles with severe associated pain for about one month prior to initiation of treatment with the therapeutic agent. The pain subsided dramatically after twelve hourly sublingual 50 microliter dosings of 10.sup.-4 mg neuraminidase in 0.1% phenol in 0.9% NaCl. The patient was pain-free for three days following the first treatment phase. Slight pain was experienced on the fourth day at which time he started sublingual administration every fifteen minutes for two hours. After this treatment, pain subsided. He was placed on a maintenance treatment regime of one dose per day for three weeks. He has remained completely free of shingles associated symptoms during the seventeen months of follow-up observation.

Detailed Description Text (15):
Three patients, ages 45, 53 and 67, were treated for chronic fatigue syndrome, a disease associated with the Epstein-Barr virus. Neuraminidase was administered at a dose of 10.sup.-4 mg sublingually 3 times a day for 3 days. All three patients

showed marked improvement with this regimen.

L6: Entry 32 of 35 File: EPAB Oct 22, 1998

PUB-NO: WO009846262A1
DOCUMENT-IDENTIFIER: WO 9846262 A1
TITLE: ANTI-INFLUENZA COMPOSITIONS SUPPLEMENTED WITH NEURAMINIDASE

PUBN-DATE: October 22, 1998

INVENTOR-INFORMATION:

NAME	COUNTRY
MATTHEWS, JAMES T	US
KILBOURNE, EDWIN D	US
JOHANSSON, BERT E	US

ASSIGNEE-INFORMATION:

NAME	COUNTRY
CONNAUGHT LAB	US
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KILBOURNE EDWIN D	US
JOHANSSON BERT E	US

APPL-NO: US09807705
APPL-DATE: April 16, 1998

PRIORITY-DATA: US84351997A (April 16, 1997)

INT-CL (IPC): A61 K 39/145; A61 K 39/39; A61 K 48/00
EUR-CL (EPC): A61K039/145; A61K039/39

ABSTRACT:

CHG DATE=19990905 STATUS=C>An anti-influenza vaccine composition wherein the improvement is that the vaccine includes, as an additive, neuraminidase (NA). The base anti-influenza vaccine can be any commercially available anti-influenza vaccine. The composition can include and be administered with an adjuvant. The vaccine composition provides protection in a host, animal or human, against influenza infection, including viral replication and systemic infection. Oral, nasal or other mucosal or per needle administration, including intracutaneous, intradermal, intramuscular, intravascular, and intravenous injections, are included.

L8: Entry 6 of 8 File: USPT Jan 23, 1979

DOCUMENT-IDENTIFIER: US 4136168 A
TITLE: Process for the preparation of neuraminidase from viral sources and methods of utilizing same

Brief Summary Text (4):
This invention relates to a new process for obtaining viral proteins from cultures of Myxovirus Influenzae. More precisely, the invention relates to a process for producing and recovering viral Hemagglutinin and viral neuraminidase in substantially pure state. The process is performed in submitting cultures of strains of Myxovirus Influenzae and namely strain of Hong-Kong virus A.sub.2 /68 (H.sub.3 N.sub.2) to the action of proteolytic enzymes obtained from cultures of Streptomyces fradiae, concentrating the fractions by diafiltration, separating the pure components by centrifugation in a discontinuous gradient of density in the presence or absence of a tensio-active agent and recovering successively viral Neuraminidase and viral Hemagglutinin. Analysis of these pure fractions shows a glycoproteinic structure. The thus obtained glycoproteins may be used in the treatment or prevention of the flu in human or veterinary medicine. They are incorporated in pharmaceutical compositions either separately or in combination, in admixture with a pharmaceutical inert non-toxic carrier suitable for parenteral, rectal, sublingual or permucous adminstration.

Brief Summary Text (30):
For this purpose, the neuraminidase, obtained according to the procedure of this invention, from cultures of the 'flu virus, is presented in the form of pharmaceutical preparations, more particularly solid, liquid or gaseous preparations for aerosols with a gaseous propellant such as butane or a freon, suitable for parenteral, sublingual, rectal or permucous administration.

L8: Entry 5 of 8 File: USPT Mar 25, 1980

DOCUMENT-IDENTIFIER: US 4195076 A
TITLE: Process for the preparation of hemagglutinin from viral sources and methods of utilizing same

Brief Summary Text (7):
More precisely, the invention relates to a process for producing and recovering viral Hemagglutinin and viral neuraminidase in substantially pure state. The process is performed in submitting cultures of strains of Myxovirus Influenzae and namely strain of Hong-Kong virus A.sub.2 /68 (H.sub.3 N.sub.2) to the action of proteolytic enzymes obtained from cultures of Streptomyces fradiae, concentrating the fractions by diafiltration, separating the pure components by centrifugation in a discontinuous gradient of density in the presence or absence of a tensio-active agent and recovering successively viral Neuraminidase and viral Hemagglutinin. Analysis of these pure fractions shows a glycoproteinic structure. The thus obtained glycoproteins may be used in the treatment or prevention of the flu in human or veterinary medicine. They are incorporated in pharmaceutical compositions either separately or in combination, in admixture with a pharmaceutical inert non-toxic carrier suitable for parenteral, rectal, sublingual or permucous administration.

Brief Summary Text (31):
As bacterial adjuvent, they may be utilized pure or raw proteins obtained from cultures of staphylococci, Neisseria, Klebsiella or micrococci. For this purpose, the neuraminidase, obtained according to the procedure of this invention, from cultures of the 'flu virus, is presented in the form of pharmaceutical preparations, more particularly solid, liquid or gaseous preparations for aerosols with a gaseous propellant such as butane or a freon, suitable for parenteral, sublingual, rectal or permucous administration. The neuraminidase obtained according to the above defined process is administered preferably in the form of an aerosol formulation containing an aqueous diluent a gaseous propellent.

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L11: Entry 19 of 20 File: USPT Sep 23, 1997

DOCUMENT-IDENTIFIER: US 5670488 A
TITLE: Adenovirus vector for gene therapy

Detailed Description Text (9):
Even if efficient DNA integration could be achieved using viruses, the human genome contains elements involved in the regulation of cellular growth only a small fraction of which are presently identified. By integrating adjacent to an element such as a proto-oncogene or an anti-oncogene, activation or inactivation of that element could occur leading to uncontrolled growth of the altered cell. It is considered likely that several such activation/inactivation steps are usually required in any one cell to induce uncontrolled proliferation (R. A. Weinberg (1989) Cancer Research 49:3713), which may reduce somewhat the potential risk. On the other hand, insertional mutagenesis leading to rumor formation is certainly known in animals with some nondefective retroviruses (R. A. Weinberg (1989); Payne, G. S. et al. (1982) Nature 295:209), and the large numbers of potential integrations occurring during the lifetime of a patient treated repeatedly in vivo with retroviruses must raise concerns on the safety of such a procedure.

Detailed Description Text (18):
Adenovirus--Defective adenoviruses at present appear to be a promising approach to CF gene therapy (Berkner, K. L. (1988) BioTechniques 6:616). Adenovirus can be manipulated such that it encodes and expresses the desired gene product, (e.g., CFTR), and at the same time is inactivated in terms of its ability to replicate in a normal lyric viral life cycle. In addition, adenovirus has a natural tropism for airway epithelia. The viruses are able to infect quiescent cells as are found in the airways, offering a major advantage over retroviruses. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis. 109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

Detailed Description Text (115):
The entire epithelium of one nasal cavity was used in each monkey. A foley catheter (size 10) was inserted through each nasal cavity into the pharynx, inflated with 2-3 ml of air, and then pulled anteriorly to obtain tight posterior occlusion at the posterior choana. Both nasal cavities were then irrigated with a solution (.about.5 ml) of 5 mM dithiothreitol plus 0.2 U/ml neuraminidase in phosphate-buffered saline (PBS) for five minutes. This solution was used to dissolve any residual mucus overlaying the epithelia. (It was subsequently found that such treatment is not required.) The washing procedure also allowed the determination of whether the balloons were effectively isolating the nasal cavity. The virus (Ad-.beta.-Gal) was then slowly instilled into the right nostril with the posterior balloon inflated. The viral solution remained in contact with the nasal mucosa for 30 minutes. At the end of 30 minutes, the remaining viral solution was removed by suction. The balloons were deflated, the catheters removed, and the monkey allowed to recover from anesthesia. Monkey A received the CsCl-purified virus (.about.1.5 ml) and Monkey B

received the crude virus (.about.6 ml). (note that this was the second exposure of Monkey A to the recombinant adenovirus).